

Serial No. 09/204,236
AR138X (269/290)

REMARKS

The Rejections

Claim Rejections - Non-Statutory Double Patenting

Claims 90-107 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-177 of copending Application No. 09/159,105 (see WO 99/14998) or continuation/divisional thereof, in view of Feghali et al. Medline 98242495. Claims 1-177 are said to be drawn to treatment of sensorineurotrophic hearing loss which is one of the neurological disorders generically embraced by the instant claims, as evidenced by Feghali that sensorineural hearing loss is a neurological disorder treatable by neurotrophic factors. The neurotrophic factors of SN 09/159,105 generically embraced the instantly claimed compounds.

Applicants respectfully request that this rejection be held in abeyance until such time as the '105 patent application is allowed and issues as a patent, and claims in the instant application are found to address allowable subject matter. At that time, any allowed and issued claims should be examined with regard to the instant pending claims. Applicants will then submit an appropriate terminal disclaimer, if and as warranted.

In the meantime, Applicants note for the record their disagreement with the rejection even at the present time. Most of the claims of the '105 application are far broader than the instant pending claims. There is nothing of record that indicates that the broad claims relating to treatment of sensorineural hearing loss would lead one of ordinary skill in the art

Serial No. 09/204,236
AR138X (269/290)

to expect that the specific instant group of compounds would be useful in treating neurological disorders specifically by stimulating growth of damaged peripheral nerves or promoting neuronal regeneration. At best, the '105 claims would render the instant claimed inventions obvious to try, but not obvious.

Feghali discusses the potential use of neurotrophic factors to treat sensorineural hearing loss. Such hearing loss, however, is specifically ascribed by Feghali to relate to hair cell damage and loss of auditory hair cells. Again, there is nothing of record that would lead one of ordinary skill to believe that compounds useful as suggested in Feghali would be useful in treating neurological disorders specifically by stimulating growth of damaged peripheral nerves or promoting neuronal regeneration.

Applicants respectfully request that this rejection be reconsidered and withdrawn, or at least held in abeyance until allowable claims are determined.

Claim Rejections - 35 U.S.C. § 103(a) or Non-Statutory Double Patenting

Claims 90-107 are provisionally rejected under 35 U.S.C. § 103(a) or under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the reference of the claims of Hamilton U.S. Pat. No. 5,721,256, or 5,874,449, or 5,968,957, in view of SN 09/159,105 and Feghali et al. The Hamilton patents are said to disclose and claim the instant method of treating neurological disorder with neurotrophic compounds. See '256 claim 13; '449 claims 20, 25, 29, and 33; and '957 claims 17-20. The Hamilton patents are said to disclose all the elements of the claims except the neurotrophic agent are structurally analogous to the claimed compounds. SN 09/159,105

Serial No. 09/204,236
AR138X (269/290)

taught in claims 1-177 analogous treating of neurotrophic hearing loss, the '256, '449, and '957 compounds/neurotrophic agents are alternative choices for the instantly claimed compounds. The office action states that one of ordinary skill would be motivated to employ a structurally similar known alternative for the generic neurotrophic factor related pathology as the instant claims.

Applicants respectfully disagree.

First, the instant claims all address methods of treating a neurological disorder, comprising administration of a compound according to the recited formula in order to stimulate growth of peripheral nerves or to promote neuronal regeneration. In contrast, many of the cited claims broadly relate to methods of effecting neuronal activity. See '256 patent claim 13; '449 patent claim 25; and '957 claims 17-20. There is absolutely no basis in the art of record to conclude that one of ordinary skill in the art would consider that the instant compounds specifically would be particularly useful for treating neurological disorders by stimulating growth of peripheral nerves or promoting neuronal regeneration.

Further, the structure of the compounds used in the instant claims is distinguishable from the compounds in the cited references.

For example, in the instant claims, the heterocyclic ring is a pyrrolidine. The substituent connecting the carbon in the pyrrolidine ring to the carboxylic acid isostere is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkylene, C₂-C₁₀ alkenylene, and C₂-C₁₀ alkynylene.

Serial No. 09/204,236
AR138X (269/290)

In contrast, the '256 patent, claim 13, and the '957 patent claims 17-20 all relate to compounds wherein the same carbon of the pyrrolidine ring is always attached to a -COO- substituent. And similarly, the '449 patent claims 20, 25, 29 and 30 all relate to compounds with either pyrrolidine or piperidine rings, wherein the subject ring carbon is necessarily attached to a -COS- or -CSS- substituent. This carboxylate, carboxylsulfide or thiocarboxylsulfide group -- required by each of the cited claims -- is necessarily missing from most of the compounds in the instant claims. Thus, there is no basis in the cited claims for one of ordinary skill in the art to expect that the compounds of the instant claims would provide the claimed effect.

The cite to Hamilton SN 09/159,105 adds little of substance to the record. Even if the '105 claims taught that the cited compounds/neurotrophic agents are alternative choices for treating neurotrophic hearing loss, there is no basis to conclude that one of ordinary skill in the art would necessarily expect the particular compounds in the instant claims to treat neurological disorders specifically by stimulating growth of peripheral nerves or promoting neuronal regeneration. At most, Hamilton would make the instant specific inventions obvious to try, rather than obvious. And there is absolutely no motivation in the cited prior art to use the specific compounds as claimed.

Thus, one of ordinary skill in the art would not expect from the cited references that the compounds in the instant claims would provide the claimed results. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Serial No. 09/204,236
AR138X (269/290)

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 90-107 are rejected under 35 USC § 112, second paragraph, as being indefinite. The scope of the claims is said to be unclear. "Are they 'carboxylic acid' and carboxylic acid isosters? Or are they including 'carboxylate' also. Please note that the cyclic moieties and isosteric structures in claims 90 and 99 included both 'carboxylic acid' and 'carboxylate' i.e. esters, amides etc." The office action states that it is clearly known in the art that "carboxylic acid" bioisosteres are distinct from "carboxylate" and that the concept has been well taught in the art, citing King p. 208 and Patani p. 3163-64 and 3169. The claims included in the term "carboxylic acid isostere" choices of ester and amides are self contradictory and confusing.

Applicants respectfully disagree. In context, and in light of the specification, one of ordinary skill in the art would understand what is meant by the claim terms "carboxylic acid isostere" or "carboxylic acid or carboxylic acid isostere."

First, Applicants respectfully request that, if this rejection is maintained, the Examiner point out specifically what term or terms are deemed to be unclear with regard to the scope of the claims. Applicants assume in the meantime that the terms of concern are "carboxylic acid isostere" in claim 90, and "carboxylic acid or carboxylic acid isostere" in claim 99.

In claim 90, the term "carboxylic acid isostere" would be clearly understood, in context, to one of ordinary skill in the art -- isosteres of carboxylic acid, potentially substituted as claimed. The term "isostere" is a term of art, which would be readily

Serial No. 09/204,236
AR138X (269/290)

understood by one of ordinary skill in the art. And an isostere would normally be "of" a particular moiety. Hence, "carboxylic acid isostere" would readily be understood to refer to isosteres of carboxylic acid.

In claim 99, the term "carboxylic acid or carboxylic acid isostere" would be clearly understood by one of ordinary skill in the art. This term, in context, refers to carboxylic acid or an isostere of carboxylic acid, again optionally substituted as claimed. For the very same reasons, this term would be readily understood by one of ordinary skill in the art.

King and Patani are consistent with this position. For example, the office action notes that carboxylic acid bioisosteres are distinct from carboxylate. However, the same moiety can be an isostere to more than one other moiety. For example, King at 208 notes that, as ring equivalents, -S- can serve as an isostere of -CH=CH-, or it can serve as an isostere of -O-, or -NH-. As a bivalent isostere, -S- correlates to -NH-, -O-, or -CH₂-.

Similarly, Patani at 3168 discusses various types of carboxylate group bioisosteres – replacements of only the hydroxyl portion, or of both the hydroxy and carboxyl fragments.

In fact, and of particular relevance, Table 43 of Patani, on page 3168, lists both carboxylic acid and carboxylate as "carboxylic acid bioisosteres."

Thus, while the term isostere is readily understood by one of ordinary skill in the art, there is inherently some degree of flexibility in determining exactly what is a isostere for a particular fragment. Nevertheless, in context, one of ordinary skill in the art would readily understand the terms of the instant claims, and the intended scope of the terms in those claims.

Serial No. 09/204,236
AR138X (269/290)

Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

Claims 90-107 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hamilton U.S. 5,721,256 in view of King or Patani. Claims 90-107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 13 of the '256 patent, in view of King or Patani. The office action notes that the "carboxylate" isosteres are *prima facie* obvious over the prior art. The replacement of a carboxyl or carbonyl moiety of a biologically active compound with a conventional "bioisosteric replacement" is said to be *prima facie* obvious because artisan in the field would recognize that such modification is a rational approach in drug design to gain more useful compounds.

Applicants respectfully disagree. First, the Examiner sets forth what might be a perfect argument that the instant claims may be "obvious to try," though they are not obvious over the prior art. Second, there is no motivation provided by the prior art to make the specific inventions embodied by the instant claims. Third, the particular use claimed is not obvious from the use disclosed in the prior art of record.

Especially when using non-classical isosteres, such as many of the isosteres suggested in the instant claims, there is certainly no guarantee that an isostere will produce the desired effect. Because of the complexities of molecular structure and bioactivity generally, clearly there may at least be significant changes in selectivity, toxicity, and metabolic stability when an isostere is substituted in an active compound. See, e.g., King

Serial No. 09/204,236
AR138X (269/290)

at 207. For example, Patani at 3163 reports failing "to identify a more potent bioisostere because of the inability to attain optimal binding geometry." Thus, while isosteric substitutions may present modifications that are obvious to try alternatives, one of ordinary skill in the art would not expect that a particular isostere necessarily would produce the desired efficacy. In effect, the use of isosteres presents the researcher with 'educated guesses' in an attempt to find further active compounds. But isosteres do not by any reasonable expectation provide certain results.

Second, there is absolutely no motivation or incentive for one of ordinary skill in the art to prepare and use the claimed compounds for the claimed efficacy. A *prima facie* case of obviousness requires that the prior art provide some suggestion or incentive to make the claimed substitution. *In re Grabiak*, 769 F.2d 729, 731-32, 226 U.S.P.Q. 870, 872 (Fed. Cir. 1985).

The structure of the compounds used in the instant claims is distinguishable from the compounds in claim 13 of the '256 patent. For example, in the instant claims, the substituent connecting the carbon in the pyrrolidine ring to the carboxylic acid isostere is selected from the group consisting of a bond, C₁-C₁₀ straight or branched chain alkylene, C₂-C₁₀ alkenylene, and C₂-C₁₀ alkynylene. In contrast, in the '256 patent, claim 13 relates to compounds wherein the same carbon of the pyrrolidine ring is always attached to a -COO- substituent. This carboxylate group -- required by the cited claim -- is necessarily missing from most of the compounds in the instant claims. Thus, there is no basis in the cited claims for one of ordinary skill in the art to expect that the compounds of the instant claims would provide the claimed effect.

Serial No. 09/204,236
AR138X (269/290)

Third, as discussed above, the instant claims address methods of treating a neurological disorder, comprising administration of a compound according to the recited formula in order to stimulate growth of peripheral nerves or to promote neuronal regeneration. In contrast, the '256 patent claim 13 broadly relates to a method of effecting neuronal activity. There is no basis in the art of record to conclude that one of ordinary skill in the art would consider that the instant compounds specifically would be particularly useful for treating neurological disorders by stimulating growth of peripheral nerves or promoting neuronal regeneration. And as discussed above, King and Patani simply offer "obvious to try" alternatives, rather than alternatives that one of ordinary skill in the art would expect necessarily to be able to use successfully.

Thus, one of ordinary skill in the art would not expect from any combination of the cited references that the compounds in the instant claims would provide the claimed results. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Bull et al WO 99/45006

The Office Action draws attention to Bull et al WO 99/45006, especially the compounds of p. 76 example 35, and preparation 49 on page 154. The Office Action notes that an interference potentially may be required.

Applicants respectfully disagree. There is no suggestion in the cited portion of Bull that the compositions included in the instant claims have the particular claimed pharmaceutical properties or use. Further, the Examiner points to no claims in Bull that would support an interference.

Serial No. 09/204,236
AR138X (269/290)

Applicants respectfully request that this issue be reconsidered.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to enter the amendments, to reconsider and withdraw the rejections of record, and to issue a Notice of Allowance.

The Examiner is welcome to telephone the undersigned attorney directly if warranted, here in Washington, D.C. at (202) 974-6004.

Respectfully submitted,

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